REMARKS

Claims 1-24 were originally filed with this application. In a Preliminary Amendment filed January 23, 2004, claims 1-13 were canceled, claims 14-24 were amended, and claims 25-28 were added. In the current Response, claims 14 and 15 are amended, claims 15-28 remain as previously presented, and the Specification has been amended to include the heading "BRIEF DESCRIPTION OF THE DRAWINGS." Reconsideration of the present application in view of the above amendments and following remarks is respectfully requested.

Rejection Under 35 U.S.C. § 112, first paragraph

Claim 14 has been rejected under 35 U.S.C. § 112, first paragraph, because, according to the Office Action, the specification, while being enabling for a statin as a water insoluble active principle, does not reasonably provide enablement for any active principle.

Claim 14 is directed to a pharmaceutical composition comprising a therapeutically effective amount of an active principle and a self micro-emulsifying carrier. Applicant's specification enables the composition for any principle, as demonstrated by example 4.

Example 4 demonstrates that the microemulsion area increases significantly when CAPRYOL 90 or CAPRYOL PGMC are used as the surfactant, regardless of the active ingredient. The micro-emulsion area is broader when caprylic ester of propylene glycol is used instead of a lauric ester of propylene glycol or oleic ester of polyglycerol. (See paragraphs 104-105 of the application as published.) The dissolution of the hydrophobic active principles are significantly improved when CAPRYOL 90 or CAPRYOL PGMC are present.

For instance, the shaded area of Figures 4 and 5 correspond to the area of micro-emulsion when CAPRYOL 90 or CAPRYOL PGMC are used as the surfactant (formulas 2 and 3 respectively). The shaded area of Figures 4 and 5 is significantly larger than that of

Figure 3 (formula 1), which represents a composition comprising a laurate of propylene glycol, for the same ratio TA/CoTA.

Applicants also assert that the microemulsion area of formulas 2 and 3 are broader than that of formula 4 (oleic esters of polygycerol). Regretably, at the time of filing of the instant application, the incorrect figure was included as figure 6 (figure 6 is attached hereto). Figure 6 as filed actually depicts a diagram of a formula including lauroglycol 90 as a surfactant with a ratio TA/CoTA of 4. Applicants submit herewith as rebuttal evidence to the enablement rejection the figure corresponding to formula 4 of example 4 of the instant specification.

This data indicates that the composition of claim 14 is effective regardless of the active ingredient. Based on the results depicted in Figures 4 and 5, the increased dissolution of the hydrophobic active principles will occur regardless of the active ingredient. The micro-emulsion area shaded in Figures 4 and 5 would remain consistent regardless of the active ingredient present in the composition. A person of ordinary skill in the art to which the invention pertains will understand that the dissolution of the hydrophobic active principles will occur with any active ingredient when the surfactant used is CAPRYOL 90 or CAPRYOL PGMC.

Consequently, for all of the above reasons, Applicants respectfully submit that claim 14 satisfies 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. §103(a)

Rejection of claim 14-17, 24-25, and 27 as being unpatentable over Farah et al.

The Examiner rejected claims 14-17, 24-25, and 27 under U.S.C. §103(a) as being unpatentable over Farah et al. (US 6,054,136). Specifically, Farah et al. teaches a micro-emulsifying drug delivery system comprising an active ingredient, a lipophilic phase, a surfactant, and a co-surfactant.

The instant claims

The presently rejected claims are directed to, in relevant part:

A pharmaceutical composition comprising (a) a therapeutically effective amount of an active principle and (b) a self micro-emulsifying carrier, said self micro-emulsifying carrier comprising:

(i) a lipophilic phase comprising a mixture of glycerol mono-, di- and triesters and of PEG mono- and diesters with at least one fatty acid chosen from the group consisting of C_8-C_{18} fatty acids;

(ii) a surfactant phase comprising a mixture of glycerol mono-, di- and triesters and of PEG mono- and diesters with caprylic acid (C_8) and capric acid (C_{10}); and

(iii) a co-surfactant phase comprising at least one ester of a polyvalent alcohol with at least one fatty acid chosen from a group consisting of **propylene glycol monocaprylate**; said surfactant and co-surfactant being in a ratio by weight between 0.2 and 6.

Argument

Farah et al. teaches the use of caprylic acid (C_8) and capric acid (C_{10}) only. Farah et al. does not teach or suggest the use of **propylene glycol monocaprylate**, as in Applicant's co-surfactant phase of claim 14 (see claim 14, iii). Farah et al. discloses the use of ethyl diglycol (TRANSCUTOL, col. 3, lines 60-64), lauric esters of propylene glycol (LAUROGLYCOL, col. 3, lines 65-66), and oleic esters of polyglycerol (PLUROL OLEIQUE, col. 4, lines 1-4), but Farah et al. does not teach the use of **propylene glycol monocaprylate** as a co-surfactant.

As shown by figures 3-5, the use of caprylic esters of propylene glycol as a co-surfactant result in an *unexpected* increased rate of dissolution of the active principle, and therefore an increase in the available active principle and thus rate of absorption over the use of lauric esters and oleic esters of polyglycerol used by Farah et al. Further, Farah et al. does not suggest any motivation to use caprylic esters of propylene glycol as a co-surfactant, such as propylene glycol monocaprylate.

Applicants respectfully assert that the Examiner has failed to establish a *prima facie* case of obviousness. Consequently, for all of the above reasons, Applicants respectfully submit that clams 14-17, 24-25, and 27 are not obvious.

Rejection under 35 U.S.C. §103(a)

Rejection of claims 18-23 as being unpatentable over Farah et al. in view of Lipari et al.

The Examiner has rejected claims 18-23 under §103(a) as being unpatentable over Farah et al. (US 6,054,136) in view of Lipari et al. (WO 00/37057). According to the Examiner, a person of ordinary skill in the art would have found it obvious to combine the pharmaceutical composition teachings of Farah et al. with the statin formulation of propylene glycol monocaprylate taught by Lipari et al. because of the bioavailability of the statin what would be conferred by the formation of a microemulsion.

Applicants disagree. As discussed above, Farah et al. discloses the use of ethyl diglycol (TRANSCUTOL, col. 3, lines 60-64), lauric esters of propylene glycol (LAUROGLYCOL, col. 3, lines 65-66), and oleic esters of polyglycerol (PLUROL OLEIQUE, col. 4, lines 1-4), but Farah et al. does not teach the use of propylene glycol monocaprylate as a co-surfactant. Lipari et al. does not cure the deficiencies of Farah et al. because Lipari et al. discloses using propylene glycol dicaprylate/dicaprate, propylene glycol dicaprate and propylene glycol mono and dicaprylate as a primary solvent medium. There is no disclosure of propylene glycol monocaprylate as a co-surfactant.

Thus, a person or ordinary skill in the art, upon reading Lipari et al. in view of Farah et al. would have been discourage from following the path taken by Applicants in arriving at the claimed inventions, because neither reference teaches or suggests using propylene glycol monocaprylate as a co-surfactant. Accordingly, the combination of the references is improper and Applicants respectfully submit that clams 18-23 are not obvious.

REJECTION UNDER 35 U.S.C. §103(a)

Rejection of claims 26 and 28 as being unpatentable over Farah et al., Lipari et al. and further in view of Patel et al.

The Examiner has rejected claims 26 and 28 under §103(a) as being unpatentable over Farah et al. (US 6,054,136) in view of Lipari et al. (WO 00/37057) and further in view of Patel et al. (US 6,248,363). According to the Examiner, in addition to the

teachings of Farah et al. and Lipari et al., Patel et al. teaches that the bioavailability of simvastatin can be improved by a surfactant of lauric macrogolglycerides.

Applicants disagree. First, Applicants reiterate the arguments presented above regarding the improper combination of Farah et al. and Lipari et al. Patel et al. does not save the combination of Farah et al. and Lipari with regard to the claims as currently presented because the combination of references of which Patel et al. has asserted is improper. It is a basic tenent of patent law that references that are not properly combinable cannot be used to establish a *prima facie* case of obviousness. Futhermore, a rejection under §103(a) cannot be predicted on the mere identification of individual components of the claimed invention that appear in the prior art. This amounts to hindsight analysis and is improper.

Patel et al. does no more than provide various laundry lists of active agents and surfactants. However, there is nothing in Patel et al. that teaches or suggests the desirability of specifically using caprylic esters of propylene glycol as a co-surfactant as presently claimed. Nor does Patel et al. provide a single example demonstrating the use of a composition having a co-surfactant phase that includes propylene glycol monocaprylate. Thus, Patel et al. should not be considered enabling for the teaching for why the Examiner relies on to reject the claims as presented herein.

CONCLUSION

In view of the above remarks, reconsideration and further examination is respectfully requested.

Applicants have made a diligent effort to place the claims in condition for allowance. However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone Erika Senska, Applicants' Attorney at (518) 452-5600 so that such issues may be resolved as expeditiously as possible.

For these reasons, and in view of the above amendments, this application is now considered to be in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

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